IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Hsing-Pang Hsieh et al.	Art Unit	: 1617
Serial No.	: 10/817,490	Examiner	: Yong Soo Chong
Filed	: April 2, 2004	Conf. No.	: 2330
Title	: Treatment Of Hepatitis C Virus Infection With Sesquiterpene Lactones		

Commissioner for Patents
P.O. Box 1450
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Pursuant to the United States Patent and Trademark Office OG Notices: 12 July 2005 - New Pre-Appeal Brief Conference Pilot Program, a request for a review of a matter identified below on appeal is hereby submitted with the Notice of Appeal. Review of this identified matter by a panel of examiners ("Panel") is requested because the rejections of record are clearly not proper and without basis, in view of legal and factual deficiencies in the rejections. All rights to address additional matters on appeal in any subsequent appeal brief are hereby reserved.

Claims 1, 2, 4-8, and 27 are now pending. Claims 1 and 5 are independent. Claim 1 covers treating hepatitis C virus (HCV) infection with a sesquiterpene compound. Claim 5 covers treating HCV infection with a sesquiterpene compound featuring γ-lactone fused with a 10-membered ring.

In the final office action dated May 21, 2009 ("final Office Action"), the Examiner (1) rejected for obviousness claims 1, 2, and 5-8, relying on Hwang et al., US Patent 5,905,089 (Hwang) and Baba et al., US Patent 6,123,943 (Baba), and (2) rejected also for obviousness claims 4 and 27, relying on Hwang, Baba, and Tan et al., Nature Review, 2002, 1: 867-881 (Tan).

Applicants will first address rejection (1).

Hwang describes sesquiterpene compounds that inhibit NF-κB activity. Baba suggests use of isoquinoline compounds to treat a large number of diseases (including HCV infection) by inhibiting NF-κB activity. According to the Examiner, one skilled in the art, in view of Hwang and Baba, would have been motivated to use sesquiterpene compounds to treat HCV infection required by claims 1 and 5. See the final Office action, page 6, lines 5-7.

In response, Applicants pointed out that, given the large size of the number of diseases described in Baba and unpredictable nature of the pertinent art, one skilled in the art would not have arrived at the claimed treatment without undue experimentation. In support of their arguments, Applicants submitted a declaration by Professor Sui-Yuan Chang at National Taiwan University (copy of which is attached hereto). The declaration (1) states that one skilled in the art, in view of Hwang and Baba, would not have expected that the sesquiterpene compounds disclosed in Hwang can be used to treat viral hepatitis disclosed in Baba, including HCV infection, given the unpredictability of the medicine field, and (2) shows a sesquiterpene compound is not effective in treating CMV infection, which, like treating HCV infection, is disclosed in Baba.

In the advisory action dated November 6, 2009, the Examiner maintains his rejection on four grounds. Applicants traverse these grounds below:

I

The Examiner asserts that "the list of diseases is not very large since one of ordinary skill in the art could have readily envisioned this scenario with a reasonable expectation of success." See page 2, lines 11-12. Applicants disagree.

Baba teaches that any inflammatory disease, any autoimmune disease, and any viral disease can be treated with isoquinoline compounds via inhibiting NF-κB activity. See column 3, lines 5-15. There are a vast number of different inflammatory diseases, a vast number of different autoimmune diseases, and a vast number of different viral diseases encompasses. Applicants note that Baba also provides a list of examples of inflammatory diseases, autoimmune diseases, and viral diseases. See column 8, lines 26-46. The list includes many encompassing terms, e.g., various intractable diseases, viral hepatitis (encompassing, among others, HCV and HBV), and diabetes (encompassing Type I diabetes and Type II diabetes). Thus, even this list encompasses a large number of diseases. In short, contrary to the Examiner's assertion, the genus disclosed in Baba is very large.

As a patent, Baba understandably asserts treatment of as many diseases as possible as an effort to obtain the broadest interpretation of claim scopes, even though treatment of most of the recited diseases is clearly inoperable. It should be recognized that such an omnipotent drug does not, and cannot, exist. Indeed, Baba provides data that only show inhibition of HIV-1 LTR transcription activity by an isoquinoline compound. One of ordinary skill, in

view of this data, would have predicted with a reasonable expectation of success only that an isoquinoline compounds can be used to treat HIV infection. Absent additional data, he or she would not have been able to predict with a reasonable expectation of success that an isoquinoline compounds can be used to treat other diseases, let alone HCV infection, by inhibiting NF-κB activity. Thus, the Examiner errs in asserting that "the list of diseases is not very large since one of ordinary skill in the art could have readily envisioned this scenario with a reasonable expectation of success."

II

The Examiner also asserts that "[Baba] was used to show that nexus between NF-kB inhibitory activity and treatment of [] hepatitis. Thus, the rejection was formulated to select hepatitis from a list of diseases." See page 2, lines 9-11. It appears to be the Examiner's position that the obviousness is established regardless the number of the diseases disclosed in Baba. Again, Applicants disagree.

Baba suggests treating any inflammatory disease, any autoimmune disease, and any viral disease. Why would one skilled in the art specifically select viral hepatitis, let alone HCV, from the very large number of diseases disclosed in Baba to be treated by the compounds taught in Hwang? Clearly, the Examiner used impermissible hindsight. Namely, after knowing Applicants' claimed HCV treatment, he searched and found Hwang, which teaches sesuiterpene compounds and their inhibitory activity against NF-kB, and then, based on this prior art teaching, searched and found Baba, which mentions treating viral hepatitis with an NF-kB inhibitor.

Applicants bring to the Examiner's attention that, according to MPEP 2142, hindsight must be avoided in determining prima facie obviousness and, "[i]t is [] necessary that the decisionmaker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art." As such, without knowledge of the subject matter being claimed, one skilled in the art would have had to test an NF-kB inhibitor in treating each inflammatory disease, each autoimmune disease, and each viral disease before arriving at the claimed invention. In other words, contrary to the Examiner's belief, given the large number of diseases disclosed in Baba, the prima facie obviousness has not been established.

III

The Examiner also asserts that "[a] patent shall be presumed valid," referring to 35 U.S.C. § 282. See page 2, lines 22-25. It appears to be the Examiner's position that, whether the pertinent art is unpredictable or not, mere description of the subject matter at issue in the prior art patent is sufficient to establish prima facie obviousness.

Applicants would first like to point out that the Examiner incorrectly relies on 35 U.S.C. § 282. Since this provision is categorized in Chapter 29 entitled "Remedies for Infringement of Patent and Other Actions," it clearly concerns infringement of a patent. That is, in infringement matters, claims of an issued patent are presumed to have legal force. Here, Baba, as an issued patent, does not claim treating diseases, but only disclose it in the specification. Thus, the issue is the veracity of this particular disclosure in Baba, not the validity (i.e., legal force) of claims. Indeed, since only the claims were examined before the patent is issued, it is improper to presume the veracity of the treatment disclosed in Baba, which has nothing to do with the allowed claims in the patent.

Applicants further point out that "**mere ... description** of the subject matter [in a prior art reference] is **insufficient,** if it cannot be produced without undue experimentation." MPEP § 2121.01, emphases added. Here, Baba merely describes treating various diseases. As the pertinent art is highly unpredictable, one skilled in the art would not be able to practice the treatment without undue experimentation. Thus, contrary to the Examiner's belief, mere description of treating viral hepatitis in Baba, not even HCV infection, would not be sufficient to constitute prior art against claims 1 and 5.

IV

The Examiner declines to give any weight to Applicants' arguments relating to Professor Chang's declaration, which refutes the disclosure in Baba, on the ground that this patent is presumed to be valid. See page 2, line 26.

As discussed above, the validity of the claims in Baba has nothing to do with the veracity of the disclosure in this patent that relates to the rejected claims. Thus, the Examiner's ground is fallacious.

Even if the law required presuming that the disclosure in Baba is truthful (which Applicants do not concede), such presumption has been successfully rebutted by Professor Chang's declaration. More specifically, the declaration has manifested that the pertinent

disclosure in Baba is not correct by showing inefficacy of treating CMV infection disclosed in that patent.

Applicants would like to further point out that even if isoquinoline compounds were effective in treating HCV infection (which Applicants also do not concede), one still would not have predicted success of using sesquiterpene compounds described in Hwang in place of isoquinoline compounds to treat HCV infection. In this regard, Applicants have attached again a copy of a scientific publication, i.e., Aubin et al., J. Neurochem., 1998, 71:1635-1642 ("Aubin"), which discloses that different NF-κB inhibitors may have totally different effects in treating the same disease. More specifically, Aubin describes that aspirin and salicylate protect against MPTP-induced dopamine depletion in mice and that dexamethasone, a much more potent NFκB inhibitor, is totally ineffective against MPTP toxicity in this dopamine depletion mouse model. See the Abstract and page 1641, left column, first paragraph. Clearly, whether an NF-kB inhibitor is effective in treating a certain disease is highly unpredictable.

In sum, given the high unpredictability of the medicine field and the large number of the diseases disclosed in Baba, on skilled in the art, in view of Hwang and Baba, would not have been motivated to arrive at the treatment covered by claims 1 and 5. In other words, claims 1 and 5 are not rendered obvious by Hwang and Baba. Neither are claims 2 and 6-8, which depend from either claim 1 or claim 5.

Applicants now turn to rejection (2), i.e., rejection of claims 4 and 27 for obviousness based on Hwang, Baba, and Tan. The patentability of claims 4 and 7, dependent from claims 1 and 5, respectively, resides at lease in part in treating HCV infection with a sesquiterpene compound. As discussed above, Hwang and Baba do not teach or suggest such treatment. Tan, which merely discloses treating HCV infection using intron A, also fails to do so. Thus, claims 4 and 27 are not rendered obvious by Hwang, Baba, and Tan.

Please apply any other charges or credits to Deposit Account No. 50-4189.

Respectfully submitted,

Date: 11-23-09

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